UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 5, 2005

MEMORANDUM

SUBJECT: Risk Assessment and Science Support Branch (RASSB) Review of Registrant Responses RE: Previous RASSB Reviews of Proposed Metalworking Fluid Use (MWF) For Densil® DG 45 Fungicide (ID NO 1258-REIA; 45 % BBIT as Active Ingredient (AI))

FROM: Norm Cook, Chief 7/5/05
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510C)

TO: Marshall Swindell, Product Manager-33
Regulatory Management Branch I
Antimicrobials Division (7510C)

Chemical: N-Butyl-1,2-benzisothiazolin-3-one (098951) or BBIT

DP Barcode: None

Summary of Findings

The Risk Assessment and Science Support Branch (RASSB) is responding to Arch Chemicals, Inc's, submissions of 3/24/05 and 6/7/05 (and has re-reviewed our meeting notes for the 2/22/05 meeting with Arch as well as our previous reviews of 1/8/03 and 4/29/04). Considering these, RASSB concludes that the proposed new MWF use for BBIT (Densil® DG 45 Fungicide), although for use in "enclosed 'metalworking systems", is a candidate for consideration under the Antimicrobials Division's (AD's) new proposed draft guidance for human exposure and effects data requirements (copy attached). Under this guidance certain toxicology data requirements (i.e., chronic, second developmental, and reproductive) are "reserved" pending registrant submission and Agency review of worker exposure (e.g., handlers and machinists) data for "enclosed MWF systems". This Agency review would result in one of two outcomes:

1. Calculated worker Margin Of Exposures (MOEs) indicate there are minimal risk concerns with the proposed MWF use in "enclosed systems". Under this scenario the "reserved" toxicology data outlined above would no longer be required to support the "enclosed

MWF use"; or

2. Calculated worker MOEs indicate there are worker risks of concern with the proposed MWF use in "enclosed systems". Under this scenario the "reserved" toxicology data outlined earlier would now be required to support continued use in "enclosed MWF systems".

Relative to the above, the Agency is willing to "reserve" the following toxicology data requirements for BBIT (Densil® DG 45 Fungicide) provided the registrant develops the human exposure data shown below:

Toxicology Data To Be Reserved:

870.3700: Prenatal developmental toxicity - non-rodent (rabbit) (TGAI)
870.3800: Reproduction and fertility effects - rodent (rat) (TGAI)
870.4100: Chronic toxicity - rodent (rat) (TGAI)
870.4100: Chronic toxicity - non-rodent (dog) (TGAI)
870.4200: Carcinogenicity - two species (rat and mouse preferred) (TGAI)
870.7485: Metabolism and pharmacokinetics - rodent (rat) (PAI or PAIRA)

[TGAI = Technical Grade of the Active Ingredient; PAI = Pure Active Ingredient PAIRA = Pure Active Ingredient Radiolabeled]

Worker Exposure Data Required:

In order to reserve the above toxicology data, the following data are required for Densil® DG 45 Fungicide:[1]

A worker (e.g., handler, machinist) exposure/monitoring study, along with product use and description of human activity information, which address dermal/inhalation exposures during application and post-application scenarios for workers who treat and/or use MWFs (including machinists), or are in contact with MWFs during maintenance and repair tasks: EP - application - 875.1200 *Dermal Exposure Indoor*, 875.1400 *Inhalation Exposure Indoor*, 875.1500 *Biological Monitoring* (in lieu of, or in addition to, data generated under 875.1200/875.1400), and 875.1700 *Product Use Information*; post-application - 875.2300 *Indoor Surface Residue Dissipation*, 875.2400 *Dermal Exposure Monitoring*,, 875.2500 *Inhalation Exposure Monitoring*, 875.2600 *Biological Monitoring* (in lieu of, or in addition to, data generated under 875.2400/875.2500), 875.2700 *Product Use Information*, and 875.2800 *Description of Human Activity*.

Additional guidance is provided to data submitters as guideline references 875.1600 *Application Exposure Monitoring Data Reporting*, and 875.2900 *Exposure and Risk Assessment Calculations*. Background references for conducting exposure monitoring

1 With the exception of Product Use and Human Activity data (875.1700/875.2700 and 875.2800), which have been satisfied with submission of MRID 461527-01.

studies can be found in 875.1000 and 875.2000.

Background Information On The Proposed New MWF Use Pattern

2002: In 2002 Avecia Biocides (now Arch Chemicals, Inc.) submitted correspondence concerning a meeting held between representatives of Avecia (Arch) and Agency scientific and regulatory staff on September 25, 2002. One topic discussed was registration of Densil DG45 for use as a preservative in MWFs. In response to this correspondence, on 1/7/03 Dr. Timothy McMahon responded by reviewing the existing toxicology database for BBIT, the active ingredient in Densil® DG 45 Fungicide, and determining which data were lacking. Dr. McMahon indicated that the following toxicology studies were required for BBIT to support the MWF use pattern:

870.3700: Prenatal developmental toxicity - non-rodent (rabbit) (TGAI)
870.3800: Reproduction and fertility effects - rodent (rat) (TGAI)
870.4100: Chronic toxicity - rodent (rat) (TGAI)
870.4100: Chronic toxicity - non-rodent (dog) (TGAI)
870.4200: Carcinogenicity - two species (rat and mouse preferred) (TGAI)
870.7485: Metabolism and pharmacokinetics - rodent (rat) (PAI or PAIRA)

[TGAI = Technical Grade of the Active Ingredient; PAI = Pure Active Ingredient PAIRA = Pure Active Ingredient Radiolabeled]

2003: In 2003 (12/15/03) Avecia (Arch) responded again to the Agency by proposing to restrict the proposed MWF use to only "enclosed metalworking systems". Additionally, as requested by the Agency the registrant submitted data to conform with *Series Guidelines 875.1700/875.2700 - Product Use information,* and *875.2800 - Description of Human Activity.* These data consisted of MRID 461527-01, a study entitled: *A Description of the Proposed Use of Densil DG 45 in Enclosed Metalworking Systems.* The study data were based on industrial practices specified in the U.S. Department of Labor, Occupational Safety & Health Administration (OSHA) Metalworking Fluids Safety and Health Best Practices Manual. The technical bulletin restriction statement *"For use only in enclosed metalworking systems with local exhaust ventilation"* is consistent with current OSHA guidance for engineering controls for high production machines.

2004: On 4/29/04 RASSB responded to the 12/15/03 submission with labeling recommendations and inclusion of the Agency's assessment for the primary handler scenario for which no engineering controls are used (i.e., the manual open pour application of product to fluid concentrates in the sump reservoir at maximum use rate of 200 ppm). This primary handler assessment concluded that with use of label-specified PPE and representative CMA study unit exposure data, both the dermal and inhalation exposure risks were not of concern (i.e., MOE ≥100).2

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2 However, a final determination of the toxicology data requirements for the "enclosed MWF system" was not done.

2005: On 2/22/05 representatives of Arch and the Agency (Doreen Aviado, Norm Cook , Nader Elkassabany, Tim McMahon, , Marshall Swindell, and Martha Terry) met to discuss the proposed "enclosed MWF system" use of Densil® DG 45 Fungicide. Arch and their representatives provided an overview of enclosed MWF systems, potential exposures, and estimated risks based on a variety of models used. Discussion on the toxicology data requirements occurred with the result that Arch would submit waiver requests for the data outlined in the Agency's review of 1/7/03. Also, the registrant representatives indicated that they would make some label and technical bulletin recommendations to ensure the product will be restricted to "enclosed MWF systems".

2005: On 3/24/05 Arch responded to the 2/22/05 meeting and the Agency's previous reviews by providing: a hazards discussion to support toxicology waivers for BBIT; modified labeling and technical bulletin including all pertinent mitigation language for "enclosed MWF systems" (see summary of mitigation measures attached); and an inhalation MOE calculation for BBIT using OSHA's Permissible Exposure Limit (PEL) (MOE = approx. 7 million).

2005: On 6/7/05 Arch responded again to the 2/22/05 meeting and the Agency's previous reviews by providing MRID 465655-01, "*The Toxicological Profile of the Isothiazolin Biocides*". This document contains: a lengthy discussion of the hazards data available for BBIT as well as for related compounds (e.g., CMIT, MIT, OIT, BIT); a structure-activity relationship analysis for BBIT; and an exposure and risk assessment for BBIT.3

In closing, the above represents RASSB's review and discussion related to the use of Densil® DG 45 Fungicide in "enclosed MWF systems". If there are any questions on what is presented here, please contact RASSB.

Attachments

cc: D. Aviado
D. Edwards
N. Elkassabany
M. Hartman
T. Leighton
T. McMahon
F. Sander

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3 Only inhalation MOEs are presented, ranging from 312,000 to 7,000,000.

Exposure and Effects Data Required By USEPA To Support New Metalworking Fluids Use Pattern

PROPOSED DRAFT GUIDANCE[1]
(6/27/05)

The following overview presents the Agency's present efforts to examine Metalworking Fluid (MWF) data requirements for new active ingredients (AIs) proposed for the first time (i.e., no other uses are registered) or for amendments to existing registrations. Typically, the Agency considers the MWF use pattern a "high exposure" one for workers (e.g., handlers, machinists), but with the advent of "closed MWF systems", the Agency is reexamining the ***toxicology*** data requirements to see if a "tiered approach" should be utilized. The following represents the Agency's present thinking on this issue (and is still under discussion within the Agency):[2]

Toxicology Data:

TOXICOLOGY DATA REQUIREMENTS					
Data Requirements	Test Substance for Product to Be Supported (MP or EP)		Present MWF Require-ments	Proposed MWF (Enclosed) Require-ments[1/]	Guideline Number
	MP	EP			
Acute Testing					
Acute oral toxicity - rat	MP; TGAI	EP; MP; TGAI	R	R	870.1100
Acute dermal toxicity	MP; TGAI	EP; MP; TGAI	R	R	870.1200
Acute inhalation toxicity - rat	MP; TGAI	EP; MP; TGAI	R	R	870.1300
Primary eye irritation - rabbit	MP; TGAI	EP; MP; TGAI	R	R	870.2400

[1] This proposed guidance refers only to human exposure and mammalian toxicity data requirements; it does not address data requirements for other science disciplines (e.g., ecological effects, environmental fate, product chemistry).

[2] The Agency believes there are limited data available for dermal and inhalation exposures of workers (e.g., handlers and machinists) and, particularly, for dermal exposures. Further, there appear to be even less dermal and inhalation exposure data available for "enclosed systems".

TOXICOLOGY DATA REQUIREMENTS					
Data Requirements	Test Substance for Product to Be Supported (MP or EP)		Present MWF Require-ments	Proposed MWF (Enclosed) Require-ments[1/]	Guideline Number
	MP	EP			
Primary dermal irritation	MP; TGAI	EP; MP; TGAI	R	R	870.2500
Dermal sensitization	MP; TGAI	EP; MP; TGAI	R	R	870.2600
Acute neurotoxicity - rat	TGAI	TGAI	CR	CR	870.6200
Subchronic Testing					
90-Day oral toxicity - rodent	TGAI	TGAI	R[2/]	R[2/]	870.3100
90-Day oral toxicity - non-rodent	TGAI	TGAI	R[2/]	CR	870.3150
21/28-Day dermal toxicity	TGAI	TGAI; EP	CR	CR	870.3250
90-Day dermal toxicity	TGAI	TGAI; EP	R[2/]	R[2/]	870.2500
90-Day inhalation - toxicity - rat	TGAI	TGAI	R[2/]	R[2/]	870.3465
90-Day neurotoxicity - rat	TGAI	TGAI	CR	CR	870.6200
Chronic Testing					
Chronic toxicity - rodent	TGAI	TGAI	R	CR	870.4100
Chronic toxicity - non-rodent	TGAI	TGAI	R	CR	870.4100
Carcinogenicity - rat preferred	TGAI	TGAI	R	CR	870.4200
Carcinogenicty - mouse preferred	TGAI	TGAI	R	CR	870.4200
Developmental Toxicity and Reproduction					
Prenatal developmental toxicity - rat preferred	TGAI	TGAI	R[3/]	R[4/]	870.3700
Prenatal developmental toxicity - rabbit preferred	TGAI	TGAI	R	CR	870.3700

TOXICOLOGY DATA REQUIREMENTS					
Data Requirements	Test Substance for Product to Be Supported (MP or EP)		Present MWF Require-ments	Proposed MWF (Enclosed) Require-ments[1/]	Guideline Number
	MP	EP			
Prenatal developmental toxicity - dermal	TGAI	TGAI	CR	CR	870.3700
Reproduction and fertility effects	TGAI	TGAI	R[3/]	R[4/]	870.3800
Developmental neurotoxicity	TGAI	TGAI	CR	CR	870.6300
Mutagenicity					
Bacterial reverse mutation assay	TGAI	TGAI	R	R	Subdivision F, App. 9 870.5100
In vitro mammalian gene mutation	TGAI	TGAI	R	R	Subdivision F, App. 9 870.5300
In vivo cytogenetics (mutagenicity)	TGAI	TGAI	R	R	Subdivision F, App. 9 870.5380 870.5385 870.5395
Special Testing					
Metabolism and pharmacokinetics	PAI or PAIRA	PAI or PAIRA	R	CR	870.7485
Companion animal safety	–	Choice	--	--	870.7200
Dermal penetration	Choice	Choice	R	CR	870.7600
Scheduled controlled operant behavior	TGAI	TGAI	CR	CR	870.6500
Peripheral nerve function	TGAI	TGAI	CR	CR	870.6850
Neurophysiology: sensory evoked potentials	TGAI	TGAI	CR	CR	870.6855
Immunotoxicity	TGAI	TGAI	CR	CR	870.7800

Key:
TGAI = Technical Grade of the Active Ingredient; PAI = Pure Active Ingredient PAIRA = Pure Active Ingredient Radiolabeled;
MP = Manufacturing Use Product; EP = End Use Product.

1/ Proposed data requirements for "enclosed metalworking systems": data marked CR -- and particularly chronic, second developmental, and reproductive data -- would be reserved pending registrant submission and Agency review

of worker exposure (see below) data for "enclosed systems".
2/ 90-day dermal and inhalation studies are preferred for MWF uses; however, the Agency will utilize the 90-day oral study when these are the only 90-day data available.
3/ A combined reproduction/developmental toxicity study can be performed and is acceptable to the Agency.
4/ A combined reproduction/developmental toxicity study is preferred, but the Agency will utilize the rat developmental study when the combined study is not available.

Human Exposure Data: To support MWF use patterns (which are considered to be high exposure use patterns), the following data are typically required for the EP when, based on the pesticide's toxicity certain toxicological criteria are triggered:

A worker (e.g., handler, machinist) exposure/monitoring study, along with product use and description of human activity information, which address dermal/inhalation exposures during application and post-application scenarios for workers who treat and/or use MWFs (including machinists), or are in contact with MWFs during maintenance and repair tasks: EP - application - 875.1200 *Dermal Exposure Indoor*, 875.1400 *Inhalation Exposure Indoor*, 875.1500 *Biological Monitoring* (in lieu of, or in addition to, data generated under 875.1200/875.1400), and 875.1700 *Product Use Information*; post-application - 875.2300 *Indoor Surface Residue Dissipation*, 875.2400 *Dermal Exposure Monitoring*,, 875.2500 *Inhalation Exposure Monitoring*, 875.2600 *Biological Monitoring* (in lieu of, or in addition to, data generated under 875.2400/875.2500), 875.2700 *Product Use Information*, and 875.2800 *Description of Human Activity*.

Additional guidance is provided to data submitters as guideline references 875.1600 *Application Exposure Monitoring Data Reporting*, and 875.2900 *Exposure and Risk Assessment Calculations*. Background reference for conducting exposure monitoring studies can be found in 875.1000 and 875.2000.